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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/854,412	CONRAD, RICHARD C.	
	Examin r	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-61 are pending in the present application. This Office action is in response to Paper No. 13, filed 16 May 2003.

Response to Amendment

The rejection of claims 1-5, 10-15, 18, 22-26, 28-30, 31, 33-42, 46, 47, 50, 53, 54 56-58 and 61 under 35 U.S.C. 102(b) as being anticipated by Kearney et al. (US Patent No. 5,759,777) has been withdrawn in view of Applicant's amendment.

The rejection of claims 2-4, 16, 17, 39-41, 45, 48, 49 are 52 under 35 U.S.C. 103(a) as being unpatentable over Kearney et al has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 5, 10-15, 18, 22-27, 30, 31, 36-38, 42, 46, 47, 50, 51 56-58 and 61 under 35 U.S.C. 103(a) as being unpatentable over Kearney as applied to claims 1, 5, 10-15, 18, 22-26, 30, 31, 36-38, 42, 46, 47, 50, 56-58 and 61 above, and further in view of Jacobs et al. (Nucleic Acids Research Vol.16 no.10 1998 pp4637-4650) has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 5, 10-15, 18, 22-26, 30, 31, 36-38, 42, 46, 47, 50, 56-58 and 61 under 35 U.S.C. 103(a) as being unpatentable over Kearney et al. as applied to claims 1, 5, 10-15, 18, 22-26, 30, 31, 36-38, 42, 46, 47, 50, 56-58 and 61 above, and further in view of Conlan et al. (Biotechniques Vol.27 no.5 1999 pp955-958) has been withdrawn in view of Applicant's amendment.

The rejection of claims 7-9 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of Applicant's amendment.

Claims 1, 5, 10-15, 18, 20-26, 30, 31, 32, 36-38, 42, 46, 47, 50, 55-59 and 61 and claims 2-4, 16, 17, 27, 28, 33, 41, 45, 48, 49, 53 and 54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kearney et al. in view of Aviv et al. (PNAS Col. 69 no.6 1972 pp 1408-1412).

Response to Arguments and New Grounds of Rejection

Necessitated by Applicant's Amendment

Applicant's arguments filed 16 May 2003 will be addressed insofar as the apply to the new grounds of rejection set forth below.

Claims 1, 5, 10-15, 18, 20-26, 30, 31, 32, 36-38, 42, 46, 47, 50, 55-59 and 61 stand rejected and claims 2-4, 16, 17, 27, 28, 33, 41, 45, 48, 49, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kearney et al. in view of Aviv et al. (PNAS Col. 69 no.6 1972 pp 1408-1412).

Applicant has amended the present claims to recite a method for purifying polyA mRNA from a sample. Previously, the claims were drawn to methods for isolating polyA RNA from a sample.

Kearney et al. teaches a method for isolating poly(A) RNA comprising using a mixture of tetramethylammonium chloride (TMAC) or tetraethylammonium chloride (TEAC) as an isostabilizing agent in a mixture with guanidinium. See entire document, especially column 6. Kearney et al. teach incubating the composition for at least four hours. See column 14, line56.

The poly(A) RNA is isolated by poly(T) affixed to a solid support such as beads. Kearney et al. also disclose that heating the mixture at temperatures ranging from 40°C to 95°C. The disclosure also teaches that various concentrations of isostabilizing agent, TMAC, was used is used in concentrations from 1M to 3M. See column 36, lines and column 12, lines 20-25 and columns 8-9. Kearney et al. on column 23, starting at line 18, teach derivitization with biotintylated labels. As Applicant has argued, Kearney et al. fail to teach their method wherein the sample from which RNA is isolated comprises mRNA.

Aviv et al. teach the isolation of poly(A) rich mRNA by binding it to poly(dT)-cellulose, poly(U)-cellulose or nitrocellulose filters.

As previously stated, it would have been obvious to those of ordinary skill in the art at the time the invention was made to isolate poly(A) mRNA using a structural composition such as cellulose to which poly(T) or poly(U) is attached and stabilizing compositions such as TMAC or TEAC. It has been known in the art for more than thirty years to use poly(U)-cellulose or poly(T)-cellulose to isolate poly(A) mRNA. Given the routine nature of the technique in the art, the ordinary skilled artisan would be motivated to use a stabilizing agent such as TMAC or TEAC in order to facilitate hybridization between the poly(A) RNA and the immobilized poly(T) molecule and provide for a simplified sample preparation. Aviv et al. teach that the binding on poly(A) rich RNA to oligo (dT) cellulose to detect poly(A) regions or mRNA's. Aviv et al. further shows that oligo (dT) cellulose chromatography can be used to separate mRNA for the bulk of rRNA in a sample. See column 1. One of skill in the art would have been motivated touse TMAC and TEAC in such a method comprising separating mRNA from a sample because because the hybrid melting temperature will not be as varied when TMAC is used because

TMAC and TEAC strengthen A:T base pairs. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant has argued regarding Kearney that: (1) it does not teach each and every element of the present claims; (2) it does not provide a reasonable expectation of success; (3) it does not solve or discuss the problem associated with mRNA isolation as discussed in the declaration regarding contamination by rRNA; and (4) teaches away from the invention.

Although Kearney et al. do not teach the isolation of mRNA using TEAC and TMAC, it clearly discloses a method for the isolation of RNA generally and that reagents such as TEAC and TMAC strengthen A:T base pairs. See column 6. Aviv et al. teach a well known method wherein poly(A) rich RNA to oligo (dT) cellulose to detect poly(A) regions and isolate mRNA's. Aviv et al. teaches that mRNA may be separated from rRNA using oligo(dT) cellulose chromatography. Given the direction of Kearney et al. and the disclosure of reagents that increase A:T interactions and that A:T interactions are vital to the isolation of mRNA in Aviv et al., together Kearney et al. and Aviv et al. teach each and every limitation of the present claims and one of skill in the art would have been motivated to use TEAC and TMAC reagents to isolate mRNA and further would have reasonably expected success in the use of such methods. Moreover, although none of the samples taught in the Kearney et al. reference comprise mRNA and are particularly concerned with rRNA, there is no explicit or implicit teaching away from the combination of these references. The fundamental principles are the same. Applicant has argued that the fact that the two technologies have been known in the art for many years and have never been combined further support the fact that the present invention is not obvious. This line of argument is untenable. This is not the appropriate standard to

establish non-obviousness. The fact that no one has actually performed an invention does not preclude a rejection under 35 U.S.C. 103. Assuming *arguendo*, that applicant's proposition is correct the only applicable legal standard for rejections over prior art would be under 35 U.S.C. 102.

Applicant also argues that there would be no motivation to combine the references because as disclosed in the declaration and argued by Applicant's representative, that it was "not known, until the instant specification, that TMAC or TEAC would have the effect of reducing the amount of contaminating rRNA in the sample." First, Applicant appears to be arguing a limitation that is not in the claims. Second, as discussed above, it was known in the art that TEAC or TMAC increase A:T interactions, as disclosed by Keaney et al., and mRNA may be separated from the rRNA in a sample, as disclosed by Aviv et al. These disclosures provide sufficient motivation to combine the present references. It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, there is no comparative data to the closest prior art for the evaluation of any possible the unexpected results over the same.

Claims 1-61 rejected under 35 U.S.C. 103(a) as being unpatentable over Kearney et al. in view of Aviv et al. as applied to claims 1-5, 10-18, 20-28, 30-33, 36-38, 41, 42, 45-50, 53-59 and 61 above, and further in view of Jacobs et al. and Conlan et al.

Kearney et al. and Aviv et al. are relied upon as described above and in the prior Office action.

Jacobs et al. teach sodium citrate to anneal oligonucleotides with TEAC and TMAC to increase the stability of the duplexes. See page 4640.

Conlan et al. teach both Triton X-100 and CHAPS as non-ionic detergent. See abstract.

It would have been obvious to those of ordinary skill in the art at the time the invention was made to isolate poly(A) RNA using sodium citrate which facilitates the annealing of nucleic acids with, a structure to which poly(T) or poly(U) is attached and stabilizing compositions such as TMAC or TEAC. Jacobs et al. teach that TEAC and TMAC give added stability to nucleic acids annealed using sodium citrate solutions. One of ordinary skill in the art would have been motivated to use sodium citrate solutions to anneal the poly(A) RNA with the poly(T) molecule given the routine nature of the technique in the art. It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize detergents such as Triton X-100 and CHAPS. One of skill in the art would have been motivated to use these detergents because they are known in the art to control protein aggregation. Moreover, one of skill in the art to would have been motivate and reasonably expected success in substituting one detergent for another. In the instant case, it is within the purview of the ordinary skilled artisan to use Triton Z-100 and CHAPS instead of SDS. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant has argued that neither Jacobs et al. nor Conlon et al. cure the deficiencies of Kearney et al. Neither reference, however, is cited for the isolation of mRNA. Jacobs et al. and Conlon et al. are cited for the teachings of sodium citrate and Triton X-100 and CHAPS, respectively. The fact that neither teaches the isolation of mRNA does not preclude their applicability. Triton X-100 and CHAPS, as disclosed in Conlon et al., control protein aggregation which is important to the isolation of nucleic acids regardless of what type of nucleic acids are being isolated by one of skill in the art. Similarly, Jacobs et al. teach the use of sodium citrate to facilitate the annealing of nucleic acids. Since the method requires the annealing of poly(A) with poly(T), it would have been obvious that such a reagent would be used in the present method.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
July 23, 2003

REMY YUCEL, PH.D
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